# Stereospecific Intramolecular Arylation of 2- and 3-Pyridyl Substituted Alkylamines via Configurationally Stable α-Pyridyl Organolithiums

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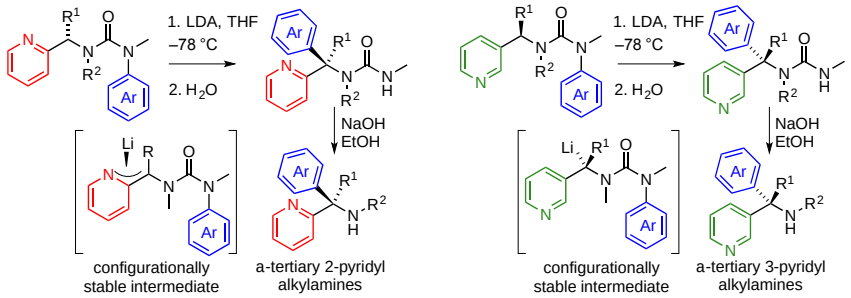
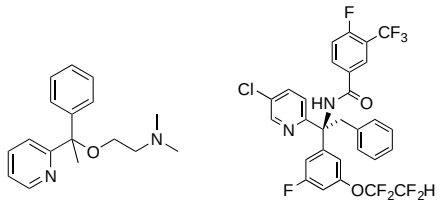
*Supporting Information Placeholder*




**ABSTRACT:** Treatment of N'-aryl urea derivatives of enantiomerically-enriched α-(2-pyridyl) and α-(3-pyridyl)alkylamines with base leads to the migration of the N'-aryl substituent from N to C in a 'non-classical' intramolecular nucleophilic aromatic substitution reaction. Both electron-rich and electron-poor rings migrate successfully. A new quaternary stereogenic centre is formed adjacent to the pyridine ring with high stereospecificity, even when the intermediate anion is a presumably planar 2-picolyllithium. Base hydrolysis of the urea gives enantiomerically enriched α-pyridylalkylamines.

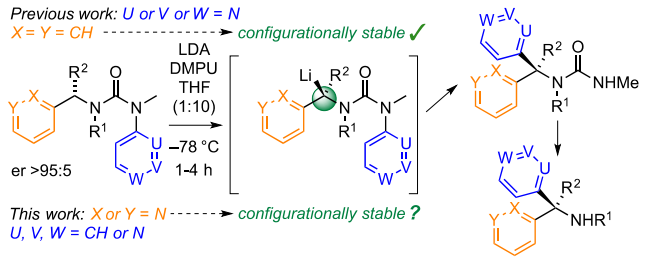
Pyridines play a vital role in medicinal chemistry,[1] being the most common heterocyclic ring encountered in small molecule drugs.[2] Substituted chiral pyridines with a stereogenic centre at the 'picolinic' position α to the pyridine ring are present in many biologically active molecules[3] and chiral ligands.[4] More specifically, congested quaternary stereogenic centres bearing both pyridine and phenyl rings are present in antihistamines such as pheniramine[5] and doxylamine[6] and in potent cholesteryl ester transfer protein (CETP) inhibitors (Figure 1.).[7]

Figure 1. Bioactive compounds with a quaternary stereogenic centre α to a pyridine ring




Methods for the synthesis of α-chiral amines bearing a pyridine ring at the stereogenic centre typically rely on auxiliaries to direct addition to, or reduction of, an intermediate imine.[8] For enantiopure α-tertiary amines with a pyridine ring as one of the substituents at the quaternary stereogenic centre (Figure 1) synthetic approaches are very limited.[9] We previously reported a stereospecific route to a subclass of these structures by intramolecular migration of pyridine rings to the α-position of lithiated urea derivatives of *N*-α-methylbenzylamine, giving α-tertiary amines after the solvolysis of the urea (Scheme 1).[9c] Stereospecificity is ensured by the configurational stability of the benzyllithium intermediates[10] on the time scale of the rearrangement reaction.[11]

Scheme 1. α-Pyridylation of chiral amines.[2]

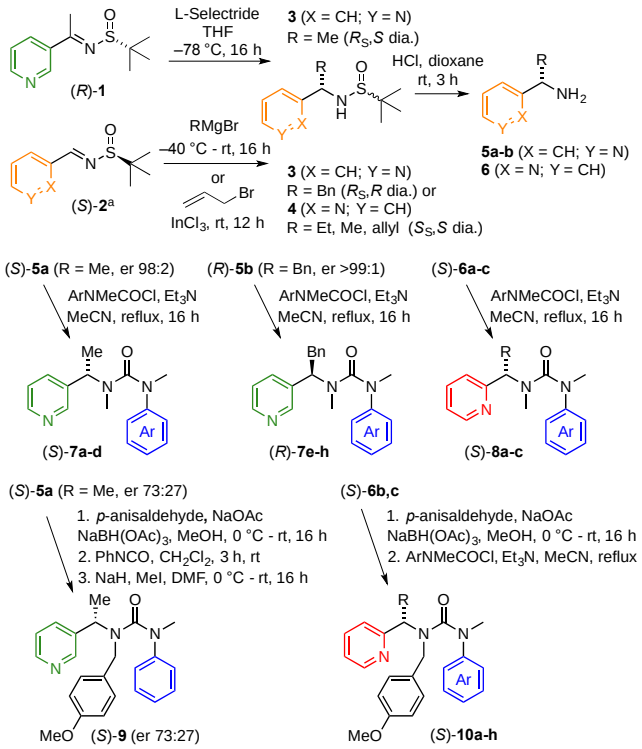



We now report a complementary method for the generation of pyridine-bearing quaternary stereogenic centers by stereospecific intramolecular arylation[12] α to 2- or 3-pyridyl substituents. The reaction is mediated by pyridine-stabilised organolithiums that exhibit remarkable

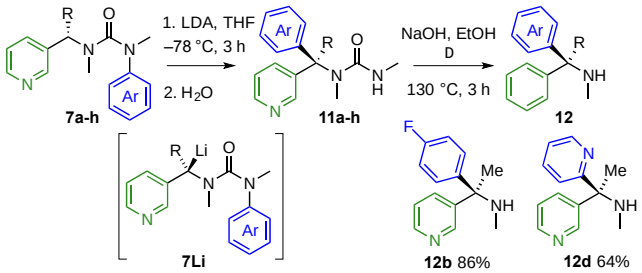
configurational stability, given the electron-withdrawing, anion-stabilising nature of the pyridyl substituents.

Chiral amine precursors **5** and **6** bearing an amino group and a 3- or 2-pyridyl substituent at the stereogenic centre were made using Ellman's N-sulfinyl auxiliary.[8] Grignard addition[13] and indium allylation[14] of N-sulfinyl aldimines **2** or diastereoselective reduction of N-sulfinyl ketimines[15] **1** gave highly enantioenriched sulfinamides **3** and **4** that were hydrolysed to chiral primary amines **5** and **6** (Scheme 2). The amines were either acylated (with *N*-methylcarbamoyl chlorides) and methylated, or reductively aminated with *p*-methoxylbenzaldehyde and acylated (with aryl isocyanates, followed by methylation, or with *N*-methylcarbamoyl chlorides), giving ureas **7-10** as starting materials for organolithium-mediated rearrangements.

Scheme 2. Synthesis of enantioenriched 2- and 3-pyridyl-substituted urea starting materials. [a]Enantiomeric sulfinimine (*R*)-**2** was used for the synthesis of (*R*)-**5**.




The 3-pyridyl-substituted urea **7a** (R = Me, Ar = Ph) was treated with LDA in THF at –78 °C (Scheme 3). After 3 hours, the reaction was quenched, and rearranged urea **11a**, in which the phenyl group had migrated from nitrogen to the position α to the pyridyl ring, was isolated in good yield without loss of enantiomeric purity (Table 1, entry 1). No additives[16] were required to maintain the stereospecificity[17] of the reaction, indicating that the presumed intermediate 3-pyridine-stabilised organolithium **7Li** does not racemise on the time scale of the rearrangement. The electron-deficient *para*-fluorophenyl, *para*-chlorophenyl, and 2-pyridyl rings of **7b-d** likewise migrated to give **11b-d** in good yields, again with full stereospecificity (entries 2-4). Urea **11d**, formed in 98:2 er, provides the first example of an α-tertiary amine derivative with both a 2- and a 3-pyridyl substituent at the stereogenic center. The tolerance of the reaction to steric hindrance[18] was explored by replacing the α-methyl substituent with a benzyl group to build structural analogues of the CETP inhibitor in Figure 1 (entries 5-8). The rearrangements of **7e-7h** were fully stereospecific, and **11e** and **11h** were formed in good yields.




Scheme 3. Stereospecific intramolecular arylation of 3-pyridine-substituted ureas. For simplicity, reactions of the *S* enantiomers are shown; in the case of **7e-h** the *R* enantiomer was used (see Table1).

**Table 1. Arylation of 3-pyridine-substtuted ureas**

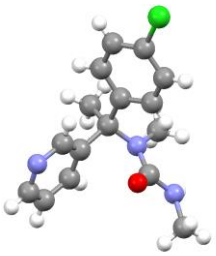
| entry | SM, er[a] | R | Ar | product, yield (%) | product, er[a] |
|---|---|---|---|---|---|
| 1 | (*S*)-**7a** 98:2 | Me | $C_6H_5$ | (*R*)-**11a** 65 | 98:2 |
| 2 | (*S*)-**7b** 98:2 | Me | 4-$FC_6H_4$ | (*R*)-**11b** 74 | 98:2 |
| 3 | (*S*)-**7c** 98:2 | Me | 4-$ClC_6H_4$ | (*R*)-**11c** 63 | 98:2 |
| 4 | (*S*)-**7d** 98:2 | Me | 2-pyridine | (*S*)-**11d** 76 | 98:2 |
| 5 | (*R*)-**7e** >99:1 | Bn | $C_6H_5$ | (*S*)-**11e** 87 | >99:1 |
| 6 | (*R*)-**7f** >99:1 | Bn | 3-$ClC_6H_4$ | (*S*)-**11f** 22 | >99:1 |
| 7 | (*R*)-**7g** >99:1 | Bn | 3-$MeOC_6H_4$ | (*S*)-**11g** 26 | >99:1 |
| 8 | (*R*)-**7h** >99:1 | Bn | 2-pyridine | (*R*)-**11h** 88 | >99:1 |

[a] Enantiomeric ratio by HPLC on chiral stationary phase.

Hydrolysis of the rearranged products under basic conditions cleaved the urea in good yield to provide α-tertiary amines **12**, illustrated by the formation of **12b** and **12d** (Scheme 3).

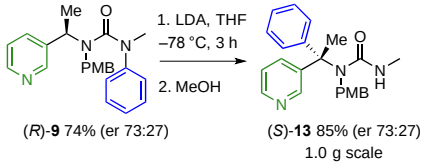
The absolute configuration of (*R*)-**11c** was determined by means of X-ray crystallography (Figure 2), and confirmed that the rearrangements of 3-pyridyl ureas proceed with retention of configuration, as has been observed in previous related rearrangements[11].

Figure 2. X-ray crystal structure of (*R*)-**11c**.

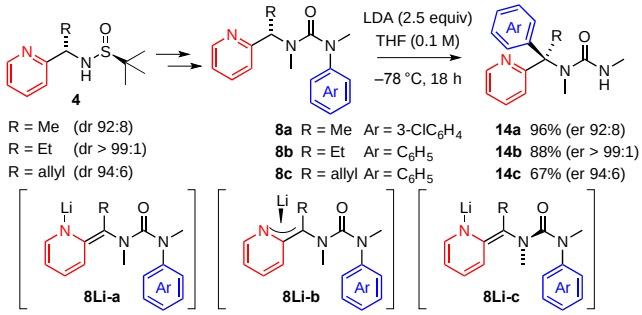


Replacing the *N*-methyl substituent with an *N*-*p*-methoxybenzyl (PMB) protecting group had no effect on the stereospecificity of the reaction: samples of (*R*)-**9** rearranged to urea **13** in good yield without loss of er on both 200 mg and 1 g scales (Scheme 4).

Scheme 4. Stereospecific intramolecular arylation of an amine with a PMB (*p*-methoxybenzyl) protecting group.



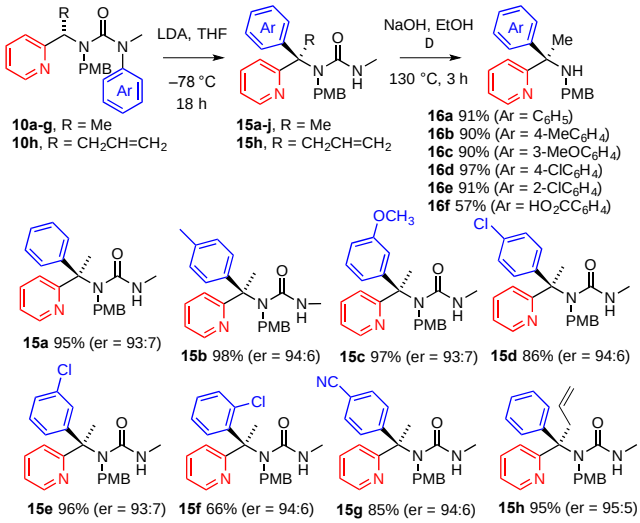

Scheme 5. Stereospecific aryl migration within 2-pyridyl-stabilized anions.




2-Pyridyl-substituted organolithiums (2-picolyllithiums) have structures best characterized as azaenolates, as represented in Scheme 5 as **8Li-a**, with a planar α-carbon and the negative charge located principally at nitrogen. [19] Urea-substituted enolates possessing other stereogenic centres undergo diastereselective intramolecular arylation,[20] but (except for examples with special structural features promoting chiral memory by hindered rotation[21]) without stereospecificity at the planar enolate carbon atom.[22] Nonetheless, treatment of the 2-pyridylurea **8a** with LDA in THF gave the rearranged compound **14a** with the same er (92:8) as the starting material (Scheme 5). Similarly, there was no loss of er in the rearrangements of ureas **8b** and **8c** bearing ethyl and allyl groups at the stereogenic centre: product ureas **14b** and **14c** were obtained in good yield and er (88%, 99:1 er and 67%, 94:6 er).

The stereospecificity of the α-(2-pyridyl)alkylamine synthesis was exploited by rearrangement of a range of *p*-methoxybenzyl-protected ureas **10a-h** built from chiral 2-pyridylamines (Scheme 6) to products **15a-h** without erosion of enantiomeric enrichment. Migrating rings with either electron-donating or withdrawing substituents at the *para* and *meta* positions all rearranged in high yield (85-98%) and good er (94:6-93:7) (**15b-15e, 15g**). The migration of aromatic groups substituted at the *ortho* position gave lower yields: with 2-chlorophenylurea **10f** the reaction remained stereospecific but the yield dropped to 66%. Attempted rearrangement of a 1-naphthyl-substituent failed. Hydrolysis of the ureas **15** under basic conditions (NaOH, EtOH) gave the valuable 2-pyridyl substituted α-tertiary amines **16** in high yields (Scheme 6).[23]

Scheme 6. Synthesis of protected tertiary α-(2-pyridyl)benzylamines by stereospecific intramolecular arylation. PMB = *p*-methoxybenzyl

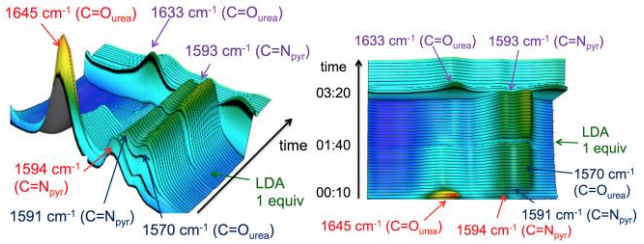



We assume that in the rearrangements of ureas **7-10** the reaction mechanism proceeds by selective deprotonation of the acidic 'picolinic' position α to the pyridyl ring to give an anionic species **7-10Li**, which undergoes the conformational reorganisation required to attack the aryl ring borne by the other nitrogen atom, but without loss of configurational integrity. A non-classical intramolecular $S_NAr$ reaction[11b] leads to the product anion, which is protonated on work-up. The intermediate anionic species **7-10Li** must retain their absolute stereochemistry on the time scale of the rearrangement. This stereospecificity is a feature of the reaction shared with other related rearrangements of lithiated ureas[9c,11a,24] (along with thiocarbamates[25] and, to a lesser extent, carbamates[16,26]), though not the cyclic ureas so far explored.[27]

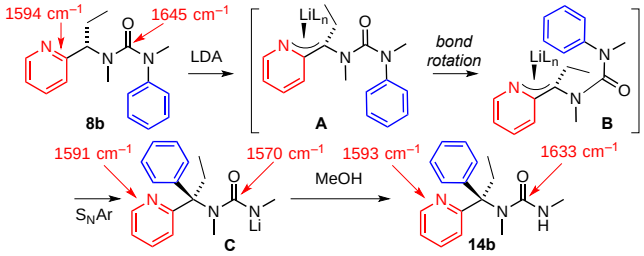
The structure of 3-picolyllithiums related to **7-8Li** have not been examined in detail, but the inability of the nitrogen atom at the 3-position to stabilize the negative charge by delocalization suggests they may have structural similarities with configurationally stable α-nitrogen substituted benzyllithiums.[3] By contrast, computational and crystallographic studies of 2-picolyllithiums related to **9-10Li**, whose negative charge is stabilized by delocalization onto the pyridyl nitrogen, show that the negative charge is principally located at the nitrogen atom, and the anion may be interpreted as a planar azaenolate, i.e. **8Li-a** (Scheme 5).[19] Given the probable planarity of the α-carbon of the intermediate anion **8Li**, possible mechanisms for stereospecificity include long-lived planar chirality within an intermediate pyridyllithium species **8Li-b** (Scheme 5)[25b-c,28] or the adoption by the urea of a chiral, twisted conformation (such as **8Li-c)** that rearranges to product faster than it can relax to an enantiomeric mixture of conformers.[21,29] Attempts to probe the role of Li in the stereospecificity were frustrated by our inability to induce rearrangement with other bases (e.g. KHMDS).

Figure 3. In situ infra-red study of the rearrangement of **8b** to **11b**. 00:10:00 – Addition of 2.5 equiv LDA starts; 01:40:00 – Addition of 1 equiv LDA complete; 03:30:00 – Reaction quenched with MeOH.

(a) (b)




Scheme 7. Proposed mechanistic pathway from **8b** to **14b**




To gain deeper insight into the mechanism of the reaction, the conversion of **8b** to **14b** in THF at −78 °C was followed by *in situ* infra-red spectroscopy (React-IR) (Figure 3 and Scheme 7). In THF at −78 °C, IR shows one C=O stretching absorption at 1645 $cm^{-1}$ and one pyridine C=N stretching absorption at 1594 $cm^{-1}$ (Figure 3a). After 10 min (00:10) an initial 2.5 equiv LDA was added, causing the C=O stretch at 1645 $cm^{-1}$ to diminish, the pyridine stretch to shift to 1591 $cm^{-1}$, and a new C=O stretch to grow at 1570 $cm^{-1}$. We assign these peaks to the rearranged, lithiated urea **C**.[11a,30] Adding another equivalent of LDA 90 minutes later (01:40) completes the reaction, as indicated by the disappearance of the C=O stretch (starting material **A**) at 1645 $cm^{-1}$ and a further increase of the C=O stretch (lithiated product **C**) at 1570 $cm^{-1}$. The detailed mechanism of formation of **C** from **B** was not explored, but previous studies[11b] have suggested that related reactions proceed by a partially concerted $S_NAr$ reaction. Finally (Figure 3b) addition of MeOH (03:20) protonates the urea anion of **C** to give **14b**, with a urea C=O stretch at 1633 $cm^{-1}$. No species identifiable as lithiated starting material **A** was observed. Product **14b** was recovered in 89% yield.

In summary, both α-(2-pyridyl) and α-(3-pyridyl) alkylamines may be arylated with total enantiospecificity at their α-position by intramolecular migration of an aryl substituent within their lithiated *N′*-aryl urea derivatives. Despite their delocalized structure, the intermediate 2-pyridyl-substituted anions are configurational stable on the time scale of the rearrangement.

## ASSOCIATED CONTENT

### Supporting Information

Full details of experimental procedures, characterization data and spectra of all new compounds; CIF file of (*R*)-**11c**. This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

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